REMARKS/ARGUMENTS

Explanation of Amendments

Applicants respectfully request entry of the above amendments.

Claims 1-3, 8, 50, and 61 have been amended. Claims 1-8, 10, 11, 47-51, 61, and 65 are currently pending. The amendments made herein were not made in response to any prior art, and no new matter has been added by way of these amendments.

Applicants note with appreciation the withdrawal of the utility rejection under 35 U.S.C. §101 relating to claims 1-8, 10, 11, 47-51, 61 and 65. Applicants further note with appreciation the withdrawal of the §112 enablement rejection as it applies to the nucleotide sequence of SEQ ID NO: 2, encoding the protein of SEQ ID NO: 1.

Rejections Under 35 U.S.C. §112

Claims 1-8, 10, 11, 47-51, 61 and 65 remain rejected under 35 U.S.C. §112, first paragraph. The Office Action asserts that the specification, while enabling for a nucleic acid of SEQ ID NO: 2 (or that encodes SEQ ID NO: 1) does provide enablement for the breadth of the claims, including fragments, derivatives, etc. thereof.

The Office Action concludes that while the specification enables one to make and use the nucleotide sequence of SEQ ID NO: 2 which encodes SEQ ID NO: 1, it would require undue experimentation to make and use the invention in a manner commensurate in scope with the claims.

Although Applicants disagree with this contention, in the interest of furthering prosecution, Applicants have made several amendments to address the Examiner's concerns. The relevant portions of Claims 1, 2, and 3 have been amended to delete the phrase, "has an activity of the human $\alpha 2/\beta 10$ heterodimer..." and replace it with the limitation, "is capable of regulating thyroidal function or promoting thyroid differentiation or proliferation". No new matter was added by way of this amendment. This specific activity finds full support and description in each of Applicants' patent applications (*see e.g.*, the 60/192,654 application at page 100, lines 7-13 *et. seq.*, and the present application at, *e.g.*, page 103, lines 25-29).

Claims 1-8, 10, 11, 47-51, 61, and 65 continue to be rejected under 35 U.S.C. §112 second paragraph. The claims that recite "moderately" or "highly" stringent conditions (e.g., claims 1-3) are said to be indefinite.

In response thereto, Claims 1, 2, and 3 have been amended to recite the specific stringency conditions for hybridization, 42°C in a buffer comprising 0.015M sodium chloride, 0.0015M sodium citrate and 50% formamide, or at 65-68°C in a buffer comprising 0.015M sodium chloride and 0.0015M sodium citrate. Support for this amendment can be found at, *e.g.*, page 31, lines 20-33, and page 32, lines 1-3. No new matter has been added by way of this amendment.

The Federal Circuit has recently indicated that a claim which recites a genus of nucleotide sequences based on their hybridization properties:

> [M]ay be adequately described if [the claimed nucleic acid molecules] hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1327 (Fed. Cir. 2002).

In view of *Enzo Biochem, Inc.*, the nucleotide sequences recited in Claims 1, 2, and 3 are adequately described because Applicants' specification describes these hybridization conditions as "highly stringent" (*see*, *e.g.*, page 31, lines 20-33, and page 32, lines 1-3). Applicants submit that in view of the explicitly-disclosed sequences and highly stringent hybridization conditions provided in the application, claims 1, 2, and 3 thus satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Withdrawal of this rejection is respectfully requested.

Additionally, Applicants have amended Claim 2 to remove reference to a nucleotide sequence encoding a polypeptide that is at least about 70 percent identical to the polypeptide set forth in SEQ ID NO: 1. Claim 2 as amended now recites polypeptides that are at least 75 percent identical to SEQ ID NO: 1. Applicants note that approximately 80% of SEQ ID NO: 1 encodes the mature portion of the β10 polypeptide. The remainder represents the signal peptide. Applicants believe that 75% identity is an appropriate level of claim scope in view of Applicants' teachings in the specification concerning amino acid substitutions to the β10 polypeptide. Support for such substitutions can be found in *e.g.*, Figure 4, which provides a comparison between the human and mouse mature forms of the β10 polypeptide, as well as Applicants' teachings regarding conservative substitutions at page 35-43.

Claim 2 is said to remain indefinite with respect to part (d). The nature of the 'fragment of at least 16 nucleotides' is said to be unclear. This rejection is asserted to also apply to claim 3, part (f). In response thereto, Applicants have amended Claims 2(d) and 3(f) to more succinctly and accurately describe Applicants' invention. Claim 2(d) as amended now recites a nucleotide sequence comprising a fragment of at least about 16 nucleotides of SEQ ID NO: 2, or of parts (a)-(c) of Claim 2. Claim 3(f) as amended now refers to a nucleotide sequence comprising a fragment of at least about 16 nucleotides of parts (a)-(e) of Claim 3. Withdrawal is respectfully requested.

Claim 8 is said to remain indefinite for assertedly failing to adequately point out that which Applicants see as their invention. Applicants previously removed reference to "β10" in Claim 8, but the Office Action now asserts that the claim reads on production of *any* protein made by the cell. In the interest of furthering prosecution, Applicants have now amended Claim 8 to recite a process of producing a polypeptide encoded by the nucleic acid molecule of Claims 1, 2, or 3 which process comprises culturing the host cell of Claim 5 under suitable conditions to express the polypeptide, and optionally isolating the polypeptide from the culture. This amendment clarifies the polypeptide produced, and withdrawal of this rejection is requested.

Claim 61 is said to continue to be indefinite, due to recitation of the term "human β10 polypeptide". The Office Action claims that the Applicant's specification does not breathe life and meaning into this term. In the interest of expediting prosecution, Applicants have amended Claim 61 to more succinctly and accurately point out the invention. Specifically, Claim 61 now recites a vector comprising at least one nucleic acid molecule according to Claims 1, 2, or 3, and at least one nucleic acid molecule encoding human α2 polypeptide. Support for this amendment can be found throughout the specification, and now new matter has been added by way of this amendment. Withdrawal of this rejection is requested.

Rejections Under 35 U.S.C. §102

Claims 1-8, 10, 11, and 47-50 are rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Mosselman *et al.*, US 2003/0059877, published 3/27/2003. The Office Action asserts that the disclosure of Applicants' parent application (09/723,970) did not comply with the requirements of 35 U.S.C. §101 and §112, 1st paragraph. Mosselman is said to carry an effective filing date of 1/17/2001. Although not specified, this appears to be a newly-raised rejection.

Additionally, Claim 51 is rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Mosselman, and further in view of Capon, *et al.*, U.S. Patent No. 5,116,964. This also appears to be a newly-raised rejection.

Applicants note that Mosselman's corresponding PCT application, WO0/153346A1, was cited by Applicants in an IDS filed October 15, 2002. MPEP 707.07(g) cautions against piecemeal prosecution. Additionally, and as noted previously, rejections by the USPTO must be stated with particularity. *See* MPEP 707.07(d). Without explanation, page 8 of the Office Action simply asserts:

> [T]he disclosure in the parent application, 09/723,970 did not comply with the requirements of 35 U.S.C. §101 and §112, first paragraph.

No basis is given for this conclusion. As cautioned even by the Examiner on page 11 of the current Office Action, it is important to avoid "[m]erely casting aspersions" without providing factual support. If the Examiner believes that Applicants are somehow not entitled to their priority filing dates, the factual basis for such a conclusion must be set forth with particularity in the Office Action.

Although not required of Applicants at this time, in the interest of expediting prosecution, Applicants point out the following regarding their priority applications:

The present application is a continuation-in-part of U.S. Application Serial No. 09/723,970, filed November 27, 2000. U.S. Serial No. 09/723,970 fully discloses the invention as claimed in full compliance with, *e.g.*, 35 U.S.C. §101 and §112:

- The complete amino acid and nucleotide sequences of the β10 polypeptide (SEQ ID NO: 1 and SEQ ID NO: 2, respectively (*see e.g.*, Figure 1, as well as page 7, lines 11-14);
- A comprehensive list of specific, substantial, and credible therapeutic utilities (*see e.g.*, pages 101 *et seq.*);
- A full description of the α2/β10 heterodimer (*see e.g.*, page 6, lines 30-33, and page 7, lines 1-6);

- Identification of important cysteine residues present in the β10 polypeptide (*see e.g.,* Figure 3), and the putative corresponding disulfide bonds in mature human β10 polypeptide (*see e.g.,* page 15, lines 7-11).

The 09/723,970 application claims the benefit of U.S. Provisional Application Serial No. 60/199,211, filed on April 24, 2000, which similarly describes Applicants' invention in full compliance with, *e.g.*, 35 U.S.C. §101 and §112:

- The complete amino acid and nucleotide sequences of the β10 polypeptide (SEQ ID NO: 1 and SEQ ID NO: 2, respectively (*see e.g.*, Figure 1, as well as page 7, lines 4-7);
- A comprehensive list of specific, substantial, and credible therapeutic utilities (*see e.g.,* pages 101 *et seq.*);
- A full description of the α2/β10 heterodimer (*see e.g.*, page 6, lines 24-33);
- Identification of important cysteine residues present in the β10 polypeptide (*see e.g.,* Figure 3), and the putative corresponding disulfide bonds in mature human β10 polypeptide (*see e.g.,* page 15, lines 7-11)

U.S. Provisional Application Serial No. 60/192,654, filed March 28, 2000 similarly discloses Applicants' invention in full compliance with the statute:

- The complete amino acid and nucleotide sequences of the β10 polypeptide (SEQ ID NO: 1 and SEQ ID NO: 2, respectively (*see e.g.*, Figure 1, as well as page 7, lines 4-7);
- A comprehensive list of specific, substantial, and credible therapeutic utilities (*see e.g.,* pages 100 *et seq.*);
- A full description of the α2/β10 heterodimer (*see e.g.*, page 6, lines 24-33);
- Identification of important cysteine residues present in the β10 polypeptide (*see e.g.,* Figure 3), and the putative corresponding disulfide bonds in mature human β10 polypeptide (*see e.g.,* page 14, lines 25-29)

Additionally, and as noted in the above applications, cDNA encoding β10 polypeptide was deposited by Applicants with the American Type Culture Collection (ATCC) on December 28, 1999, under accession number PTA-1210.

Applicants' effective filing date is March 28, 2000, predating Mosselman's asserted §102(e) date of January 17, 2001. As outlined herein, Applicants' parent applications are in full compliance with *e.g.*, 35 U.S.C. §101 and §112, and withdrawal of the rejections based upon Mosselman *et al.* and Capon *et al.* is respectfully requested.

Claims 1-5, 7, and 11 remain rejected under 35 U.S.C.§ 102(b) over Mahairas *et al.*, Locus AQ495547.

On page 10, the Office Action asserts that Applicants have not pointed out the basis in the specification as originally filed for the assertion that cysteine residues are important for activity. Applicants note in its applications (*see e.g.*, the 09/818,954 application at page 4, lines 16-21, and the 60/192,654 application at page 6, lines 1-5) that the three cysteines C12, C36, and C40 are among the group of six cysteines which form the three disulfide cystine-knot, responsible for the overall three dimensional structure of the molecule.

The Office Action adds that the claims do not recite any specific activity, but rather only require *an activity*, which is said to encompass antibody binding. In response to this concern, Applicants have amended their claims to recite a specific, substantial, and credible utility, that is the ability of β10, when heterodimerized to human α2 polypeptide, to regulate thyroidal function or promote thyroid differentiation or proliferation.

As noted in Applicants' previous response, Mahairas describes a truncated BAC clone fragment containing a piece of human genomic DNA. The fragment in Mahairas is completely unannotated, identifies no reading frame, no cloning orientation (5' or 3'), etc. As noted in Applicants' previous response, these cysteines are encoded by exon 1, and are not present in the Mahairas sequence. Mahairas lacks any description of the mature form of the β10 polypeptide, and the polypeptide encoded by the sequence in Mahairas would simply not be able to adopt a cystine-knot configuration.

Mahairas thus does not identify each and every feature recited in the claim sought to be invalidated. *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Mahairas does not describe the identical invention in as complete detail as

contained in Applicants' claims. *See Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1920 (Fed. Cir. 1989). Lastly, as noted previously, Mahairas is not an enabling disclosure. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003) and *In re Hoeksma*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

Withdrawal of the rejection under 35 U.S.C. §102(b) in view of Mahairas is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-5, 7, and 11 remain rejected under 35 U.S.C. §103(a) as being obvious in view of Mahairas, and Claims 6, 8, and 48-50 remain rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Mahairas in view of Sibson *et al.*, WO 94/01548.

In response thereto, Applicants provide a Declaration of Chris Paszty, Ph.D. in accordance with 37 CFR §1.132.

Dr. Paszty notes that Mahairas describes a fragment of genomic DNA, having an intron and no reading frame, orientation, or annotations. According to Dr. Paszty, the sequence in Mahairas which, if translated, would encode an inactive portion of the β10 molecule, which would not be capable of folding properly. Dr. Paszty also notes that the β10 fragment in Mahairas was not obtained by cDNA cloning.

Dr. Paszty further notes that Sibson relates to completely unrelated cDNA sequences, not genomic DNA, and certain methods of producing them.

Elements of separate patents (or publications) cannot be combined when there is no suggestion of such combination anywhere in those patents (or publications). *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593, (Fed. Cir. 1987), citing *ACS Hospital Systems,* 220 USPQ 929, 933 (Fed Cir 1984). As Dr. Paszty explains in his declaration, there is simply no suggestion in Mahairas or Sibson of combining the two references.

Additionally, an analysis under 35 U.S.C. §103 requires consideration not only of whether the prior art would have suggested to one skilled in the art that they should make the claimed composition, but also whether the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), *citing In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). It should be noted that both the suggestion and the reasonable expectation of success must be founded in the

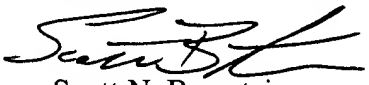
prior art, not in the applicant's own disclosure. *Id.* Dr. Paszty notes in his declaration that not only is there no suggestion in the cited references to combine Mahairas and Sibson, but further adds that even if one skilled in the art were motivated to combine these references, the combination of Mahairas and Sibson would at best result in a misfolded, inactive peptide fragment, and certainly not Applicants claimed molecules.

In view of Applicants' amendments made herein, Dr. Paszty's declaration, and the arguments presented above, withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants believe that all pending claims are now in condition for allowance, and respectfully request reconsideration.

Respectfully submitted,



Scott N. Bernstein
Attorney for Applicants
Registration No: 38,827
Phone: (805) 447-4128
Date: September 17, 2004

Please send all future correspondence to:

US Patent Operations/SNB
Dept. 4300, M/S 27-4-A
AMGEN INC.
One Amgen Center Drive
Thousand Oaks, California 91320-1799